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AGRICAN is the largest cohort worldwide assessing various tasks related to lifetime occupational history of 18 major agricultural activities and not only pesticide use. A dose–response relationship was observed with the number of cattle raised, especially for insecticide application. Prostate cancer was associated with pesticide exposure in fruit growing, not only with pesticide use but also with harvesting.

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Prostate cancer risk among French farmers in the AGRICAN cohort

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Objectives Prostate cancer is one of the most frequent cancers among men worldwide. Its etiology is largely unknown, but an increased risk has been repeatedly observed among farmers. Our aim was to identify occupational risk factors for prostate cancer among farmers in the prospective cohort study AGRICAN.

Methods Data on lifetime agricultural exposures (type of crops, livestock and tasks including pesticide use, re-entry and harvesting) were collected from the enrolment questionnaire. During the period from enrolment (2005–2007) to 31 December 2009, 1672 incident prostate cancers were identified. Hazard ratios (HR) were estimated using Cox regression analysis.

Results We found an increased risk for cattle breeders using insecticides [HR 1.20, 95% confidence interval (95% CI) 1.01–1.42] with a significant dose–response relationship with number of cattle treated (P for trend 0.01). A dose–response relationship was also observed with the number of hogs (P for trend 0.06). We found an excess of prostate cancer risk among people involved in grassland activities, mainly in haymaking (HR 1.18, 95% CI 1.02–1.36). Pesticide use and harvesting among fruit growers were associated with an elevated prostate cancer risk, with a two-fold increased risk for the largest area. For potato and tobacco producers, an elevated prostate cancer risk was observed for almost all tasks, suggesting a link with pesticide exposure since all of them potentially involved pesticide exposure.

Conclusions Our analysis suggests that the risk of prostate cancer is increased in several farming activities (cattle and hog breeding, grassland and fruit-growing) and for some tasks including pesticide use.

Key terms agriculture; exposure; farming; France; pesticide.

Prostate cancer is one of the most frequent cancers worldwide. In high-income countries (Europe, Northern America, Australia/New Zealand and Japan), it represents 23% of male cancers with >740 000 incident cases estimated in 2012 (1). However, its etiology remains largely unknown. The only well-established risk factors for prostate cancer are older age, ethnic origin (with black/sub-Saharan men at higher risk) and family history of the disease. Other risk factors are suspected like lifestyle (physical activity, alcohol consumption, smoking, diet), infections (sexually transmitted diseases and prostatitis) and hormone levels (2). Although the International Agency for Research on Cancer (IARC) has not classified any occupational exposure as a prostate carcinogen, some occupations are thought to play a role in the cancer's etiology, especially those related to heavy metals, cadmium, arsenic, diesel exhaust, polycyclic

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aromatic hydrocarbons and pesticides (3). Some meta-analyses reported an increased prostate cancer risk among farmers (4–6), which was confirmed by a more recent meta-analysis based on case–control studies (7). Three meta-analyses have assessed prostate cancer risk among pesticide users. In the first (8), a greater risk was found among workers potentially exposed to pesticides [meta-rate ratio (MRR) 1.13, 95% confidence interval (95% CI) 1.04–1.22; 22 studies], but no association was observed in the sub-group of farmers (MRR 0.97, 95% CI 0.92–1.03; 11 studies). The second review (9) was conducted among professional pesticide users such as agricultural pesticide applicators, farmers licensed to use pesticides, nursery and greenhouse workers, and employees of companies involved in spraying activities. The risk observed was greater than in the previous publication (MRR 1.24, 95% CI 1.06–1.45; 22 studies). The third analysis (10), which investigated chemical families among workers exposed to a lower number of chemicals and with a better characterization of exposure, was conducted among pesticide production employees, and concluded the risk was increased (MRR 1.28, 95% CI 1.05–1.69; 16 studies). The Agricultural Health Study, a prospective cohort of licensed pesticide applicators and their spouses in North Carolina and Iowa, observed a significant increased risk of prostate cancer among >51 000 male private applicators (RR 1.26, 95% CI 1.18–1.33; 1046 cases) after 5 years of follow-up (11) and (RR 1.19, 95% CI 1.14–1.25; 1719 cases) after 11 years (12). People involved in agriculture are exposed to many chemicals (pesticides, solvents, disinfectants, fumes), biologic (viruses, mycotoxins) and physical agents (ultraviolet light). Most studies to date have only focused on farmers or agricultural workers as a job title with no further details on specific tasks apart from pesticide use which is often limited to application on crops, with no data on other exposures to pesticides. A limited number of studies have investigated the type of animal raised or the type of crop production. Cattle breeding (13, 14) and some crops (wheat) (15) and fruit-growing) (16–18) have been associated with prostate cancer risk. To our knowledge, only six studies have investigated the role of specific tasks other than pesticide use. They were related to animal breeding (19–24) or crops (20–22, 24, 25). Except in one study (19), duration or intensity of exposure have not been studied.

Our aim was to identify possible occupational risk factors for prostate cancer in farmers, focusing on specific tasks for various crops grown or animals raised.

Methods

Population

To be included in the AGRICAN (AGRIculture and CANcer) cohort, men and women had to be aged at least 18 years, active or retired, have been affiliated with the French agricultural health insurance scheme *Mutualité Sociale Agricole* (MSA) for ≥3 years during their lifetime, and be living in one of the 11 geographical areas covered by a population-based cancer registry at the time of enrolment from 1 November 2005 to 31 December 2007. All eligible subjects received a self-administered questionnaire, including a complete job calendar with a lifetime history of occupational activities, sociodemographic characteristics, lifestyle habits and some health data. Furthermore, they were asked if they had ever worked in any of 18 specific agricultural activities (5 types of animals and 13 crops), and if they had ever performed some given tasks related to these activities (2–5 tasks, according to type of animals and crops except for field-grown vegetables and greenhouses) or other farm exposures (maintenance or repairing pesticide equipment, mechanical engineering, pesticide poisoning, etc) (Questionnaire available online: http://cancerspreventions.fr/wp-content/uploads/2015/02/questionnaire_inclusion_agrican_2005_anglais.pdf). The subjects who returned the questionnaire were included in the cohort (N=181 842). Details on materials and methods have been previously published (26).

Follow-up

Vital status was ascertained annually by using the MSA and French National Death Index (*Répertoire National pour l'Identification des Personnes Physiques*) and we identified annually any cohort members no longer residing in any participating geographical area through the MSA's and the French national postal service's (*La Poste*) databases. Cohort members were matched to cancer registries in each of the 11 geographical areas every two years to identify prostate cancer occurring between enrolment (2005–2007) and 31 December 2009. Mean duration of follow-up in the study was 3.4 years. During this period, 1672 incident prostate cancer cases were identified.

Cancers were coded according to the International Classification of Diseases for Oncology, 3rd revision (ICD-O-3). Individuals were followed until the date of prostate cancer diagnosis for cases, or – for prostate cancer-free subjects – until date of death, the date they left the study area, and the date they were lost to, or ended, follow-up (31 December 2009), whichever came first. For the present analysis, subjects were excluded if they lived in an area with no prostate cancer registry (Côte-d'Or) (N=6186, 6%), if they were diagnosed for a prostate cancer before enrolment (N=892, 1%) or could not be classified accurately for lifelong agricultural status (N=9755, 10%). After application of these criteria, 81 961 men and 1496 prostate cancer cases remained for the analysis (ICD-O-3 topography code C61). Almost all prostate cancers recorded (99%) were adenocarcinomas.

Statistical analysis

Hazard ratios (HR) with 95% confidence intervals (95% CI) were estimated by using Cox regression analysis with attained age as the underlying time scale to assess prostate cancer risk related to agricultural exposures. We considered a left-truncation at age at baseline to account for age in the modelling (27).

Ever/never exposure categories were defined from the 18 farming activities and their related tasks. We also considered pesticide use on at least one type of crop and insecticide use on at least one type of animal. Secondarily, duration of activities and tasks and intensity (largest cultivated area of the crop or highest number of animals raised) were used as categorical variables, using percentiles cut off for size and decades for duration. Categories were collapsed when the number of exposed cases was <5. For each exposure considered (related to activity or task), the reference group consisted of people who had worked on a farm but never involved in the corresponding activity.

To take into account possible correlation between farming activities, associations between each significantly associated exposure variable were additionally adjusted for other statistically significant exposures. Only crude results are presented since no substantial change (>20%) (28) was observed after adjustment for other agricultural activities or individual characteristics (educational level, smoking duration, body mass index, geographical area), except for working in wine cellars. For exposures associated with prostate cancer risk, when numbers were sufficient, we applied 10, 20, and 30 years latency periods.

Statistical analysis was performed with SAS version 9.3 (SAS Institute, Inc, Cary, NC, USA).

Results

Characteristics of the population

The median age at enrolment was 64 years [(Q1–Q3): (50–75)]. Most of the men were born in France (excluding French overseas territory) (97%). Forty-one percent had attained less than middle school grade and 10% more than high school grade. Less than half (43%) had never smoked, while 43% were overweight and 14% were obese (table 1).

Exposure to agricultural activities (animal & crops)

Almost all (87%) of the cohort had already worked on a farm during their lifetime (table 2). The most common farming activities were cattle breeding (68%), and grassland (64%) and wheat or barley (55%) farming, while <10% were involved in some other type of cultivation (peas, sunflower, tobacco, field-grown vegetables and greenhouses). A slight non-significant increased risk was associated with involvement in farming (HR 1.05, 95% CI 0.89–1.24) compared to people who never worked on a farm.

Table 1. General characteristics of men at enrolment in the AGRICAN cohort. [Q1=25th percentile; Q3=75th percentile; N=number of subjects exposed].

	Median	Q1–Q3	N	%
Age (years)	64	50–75		
Place of birth				
France (excluding overseas)			79 086	96.5
Overseas areas and other country			2873	3.5
Missing			2	<0.1
Highest grade completed				
Less than middle school			33 750	41.2
Middle school or high school			35 602	43.4
More than high school			8192	10.0
Missing			4417	5.4
Smoking status				
Never			35 495	43.3
Former			31 908	38.9
Current			10 878	13.3
Missing			3680	4.5
Body mass index (kg/m²)				
Underweight <18.5			413	0.5
Normal weight 18.5–24.9			26 418	32.2
Overweight 25.0–29.9			35 424	43.2
Obesity ≥30.0			11 199	13.7
Missing			8507	10.4

A non-significant small increase in risk was observed for four types of animal raised, (horses poultry, hogs, and cattle) from 1.06, 95% CI 0.94–1.20 to 1.16, 95% CI 0.99–1.36. The risk observed increased with the number of animals raised for cattle (≥150 cattle: HR 1.29, 95% CI 0.96–1.74; P for trend=0.08) and hogs (≥500 hogs: HR 1.40, 95% CI 0.81–2.43; P for trend=0.06) (data not shown). Among crops, only grassland was significantly associated with a greater prostate cancer risk (HR 1.16, 95% CI 1.01–1.33). A risk greater than unity was observed for nine crops: from 1.01, 95% CI 0.85–1.20 for rape to 1.17, 95% CI 0.99–1.38 for tobacco. A decreased risk was found for vineyard, corn, and field-grown vegetables.

Among farm exposures, pesticide use on crops was associated with a higher risk of prostate cancer (HR 1.10, 95% CI 0.97–1.25) especially among men who did not use protective gloves (HR 1.14, 95% CI 0.99–1.32). No dose–response relationship was observed with duration of wearing gloves. An increased risk of prostate cancer was observed among farmers with the largest fruit-growing areas (≥25 hectares: HR 1.54, 95% CI 0.85–2.79; P for trend=0.12) (data not shown).

Table 2. Agricultural activities and prostate cancer risk in the AGRICAN cohort. **BOLD** denotes statistically significant values (P<0.05). [HR=hazard ratio; 95% CI=95% confidence interval.]

	%	N cases	HR	95% CI	P for trend
Farming [a]	87.1	1338	1.05	0.89–1.24	
Agricultural activities [b]					
Animal raising					
Cattle	68.0	1008	1.16	0.99–1.36	
Sheep/goat	11.5	163	0.96	0.82–1.14	
Hogs	21.7	375	1.10	0.97–1.24	
Horses	22.3	401	1.06	0.94–1.20	
Poultry	24.0	389	1.08	0.96–1.22	
Crop production					
Grassland	64.1	935	**1.16**	**1.01–1.33**	
Vineyard	35.3	460	0.90	0.80–1.01	
Corn	43.1	548	0.99	0.88–1.11	
Wheat/barley	55.4	784	1.11	0.98–1.25	
Peas	8.4	100	1.03	0.84–1.27	
Beets	20.5	332	1.03	0.90–1.17	
Sunflower	9.7	116	1.04	0.86–1.26	
Rape	12.3	141	1.01	0.85–1.20	
Tobacco	9.3	159	1.17	0.99–1.38	
Fruit-growing	18.2	284	1.05	0.91–1.21	
Potatoes	24.5	418	1.06	0.94–1.20	
Field-grown vegetables	9.2	112	0.87	0.72–1.06	
Greenhouses	4.4	55	1.12	0.85–1.47	
Other exposures on farm					
Insecticide use on animals [c]	39.7	535	1.06	0.94–1.20	
Duration (years) of insecticide use on animals [c]					0.68
0–9	3.4	32	1.15	0.81–1.65	
10–19	4.6	40	1.14	0.82–1.57	
20–29	5.5	49	0.97	0.72–1.30	
30–39	4.9	81	1.07	0.84–1.35	
≥40	3.2	64	1.03	0.79–1.33	
Pesticide use on crops [d]	59.3	789	1.10	0.97–1.25	
Duration (years) of pesticide use on crops [d]					0.91
0–9	5.9	60	1.19	0.90–1.57	
10–19	7.6	68	1.21	0.93–1.58	
20–29	9.1	91	1.15	0.91–1.46	
30–39	9.5	139	1.00	0.82–1.22	
≥40	7.1	135	1.03	0.84–1.26	
Using gloves [d]					
Never	24.3	387	1.14	0.99–1.32	
Sometimes	17.4	189	1.04	0.87–1.24	
Always	9.0	66	1.00	0.77–1.31	
Duration (years) use of gloves [d]					0.68
Never	24.3	387	1.14	0.99–1.33	
0–9	4.5	17	0.93	0.57–1.53	
10–19	4.2	29	1.11	0.76–1.63	
20–29	3.0	25	0.85	0.56–1.28	
≥30	2.0	36	1.09	0.77–1.54	
Treatments of seeds on the farm	28.7	439	1.06	0.92–1.22	
Use of herbicides in the farmyard	61.5	766	1.02	0.89–1.17	
Maintenance of pesticide equipment	29.5	309	0.89	0.78–1.01	
Repairing pesticide equipment	9.4	84	0.85	0.68–1.07	
Mechanical engineering	26.6	270	0.98	0.85–1.13	
Pesticide poisoning	6.0	75	1.03	0.81–1.30	
Frequency – once	4.5	62	1.09	0.85–1.41	
Frequency – twice or more	1.4	13	0.80	0.46–1.38	

[a] Reference group=men who never worked on a farm.
[b] Reference group=farmers who were never involved in the corresponding activity.
[c] Reference group=farmers who did not use insecticides on animals.
[d] Reference group=farmers who did not use pesticides on crops.

Table 3. Agricultural tasks related to cattle breeding and prostate cancer risk in the AGRICAN cohort. Reference group was farmers never involved in cattle breeding. **BOLD** denotes statistically significant values (P <0.05). [HR=Hazard Ratio; CI=confidence interval; N=number of exposed cases].

	N cases	HR	95%CI	P for trend
Animal care				
Ever	909	1.15	0.98–1.35	
≥40 years [a]	214	1.15	0.94–1.40	0.84
≥150 cattle [b]	48	1.20	0.87-1.65	0.11
Milking				
Ever	723	1.14	0.97–1.34	
≥40 years [a]	92	1.17	0.91–1.51	0.36
≥150 cattle [b]	9	**1.97**	**1.01-3.86**	0.20
Insecticide use on cattle				
Ever	485	**1.20**	**1.01–1.42**	
≥40 years [a]	53	1.14	0.84–1.54	0.22
≥150 cattle [b]	22	**1.59**	**1.02–2.48**	**0.01**
Disinfection of barns				
Ever	470	**1.21**	**1.02–1.44**	
≥40 years [a]	42	1.10	0.78–1.53	0.74
Milking equipment disinfection				
Ever	407	1.15	0.96–1.37	
≥40 years [a]	23	0.88	0.57–1.35	0.86

[a] Duration categorized in decades (0–9, 10–19, 20–29, 30–39, ≥40 years).
[b] Number of cattle raised categorized in exposed subjects involved in the corresponding activity according to 25th, 50th, 75th and 90th percentile (≤24, 25–49, 50–99, 100–149, ≥150 cattle).

Exposure to animal-related tasks

Insecticide use on cattle (HR 1.20, 95% CI 1.01–1.42) and disinfection of cattle barns (HR 1.21, 95 % CI 1.02–1.44) were significantly associated with a greater risk of prostate cancer (table 3). We also observed an increased risk, albeit non-significant, for the three other tasks related to cattle (animal care HR 1.15, 95% CI 0.98–1.35, milking HR 1.14, 95% CI 0.97–1.34, and milking equipment disinfection HR 1.15, 95% CI 0.96–1.37). The risk increased with the number of insecticide-treated cattle (P for trend=0.01), with no difference according to the timing of exposure (data not shown). Likewise, milking ≥150 cattle was also associated with a greater risk (HR 1.97, 95% CI 1.01–3.86) but without a dose–response relationship (P for trend=0.20). A risk >1 was observed for all three tasks related to hog breeding (animal care HR 1.10, 95% CI 0.96–1.25, insecticide use HR 1.06, 95% CI 0.85–1.33, and disinfection of barns HR 1.09, 95% CI 0.92–1.29). For detailed results on animal-related tasks, see supplementary materials S1 (www.sjweh.fi/data_repository.php). No statistically significant associations were observed for tasks related to other types of animals (sheep/goat, horses, and poultry) (data not shown).

Exposure to crop-related tasks

Making hay in grassland was associated with a significant increase in prostate cancer (HR 1.18, 95% CI

Table 4. Agricultural tasks related to crops and prostate cancer risk in the AGRICAN cohort. Reference group was farmers never involved in the corresponding activity. **BOLD** denotes statistically significant values (P<0.05). [HR=hazard ratio; 95% CI=95% confidence interval; N=number of exposed cases].

	N cases	HR	95% CI	P for trend
Grassland				
Herbicide use				
Ever	310	1.14	0.96–1.34	
≥40 years [a]	34	0.86	0.60–1.23	0.62
≥60 hectares [b]	21	1.11	0.71–1.74	0.68
Haymaking				
Ever	857	**1.18**	**1.02–1.36**	
≥40 years [a]	175	1.14	0.94–1.39	0.15
≥60 hectares [b]	44	**1.52**	**1.10–2.09**	0.06
Wheat/barley				
Seed treatment				
Ever	373	**1.16**	**1.01–1.34**	
≥40 years [a]	52	1.06	0.80–1.42	0.73
Sowing				
Ever	582	1.12	0.99–1.27	
≥40 years [a]	88	1.13	0.89–1.42	0.43
≥75 hectares [c]	10	0.83	0.44–1.55	0.55
Pesticide use				
Ever	471	**1.17**	**1.03–1.34**	
≥40 years [a]	66	1.28	0.99–1.67	0.26
≥75 hectares [c]	11	1.09	0.60–1.98	0.47
Harvesting				
Ever	638	1.13	1.00–1.28	
≥40 years [a]	102	**1.27**	**1.02–1.58**	0.18
≥75 hectares [c]	17	1.11	0.68–1.80	0.74
Sunflower				
Seed treatment				
Ever	13	0.71	0.41–1.23	
Sowing				
Ever	91	1.09	0.88–1.36	
≥30 years [a]	8	1.13	0.56–2.26	0.26
≥20 hectares [d]	5	0.56	0.23–1.36	0.55
Pesticide use				
Ever	89	1.19	0.96–1.48	
≥30 years [a]	7	1.17	0.55–2.45	0.12
≥20 hectares [d]	6	0.80	0.36–1.78	0.61
Harvesting				
Ever	88	1.12	0.90–1.39	
≥30 years [a]	7	1.13	0.54–2.38	0.09
≥20 hectares [d]	6	0.74	0.33–1.66	0.71
Tobacco				
Sowing				
Ever	140	**1.26**	**1.06–1.51**	
≥40 years [a]	11	1.26	0.69–2.28	**0.03**
≥5 hectares [e]	9	0.96	0.50–1.85	0.76
Pesticide use				
Ever	85	1.24	0.99–1.54	
≥40 years [a]	6	1.63	0.73–3.65	**0.02**
≥5 hectares [e]	7	1.98	0.94–4.17	**0.04**
Harvesting				
Ever	140	**1.29**	**1.08–1.54**	
≥40 years [a]	9	1.41	0.73–2.72	0.08
≥5 hectares [e]	6	1.14	0.51–2.53	0.42
Fruit growing				
Pruning				
Ever	146	1.05	0.88–1.26	
≥40 years [a]	20	1.15	0.74–1.80	0.14
≥25 hectares [f]	6	1.62	0.72–3.61	0.12
Pesticide use				
Ever	112	1.19	0.97–1.45	
≥40 years [a]	11	1.20	0.66–2.17	0.13
≥25 hectares [f]	7	**2.28**	**1.08–4.80**	**0.02**
Harvesting				
Ever	209	1.13	0.97–1.32	
≥40 years [a]	35	1.31	0.93–1.84	**0.04**
≥25 hectares [f]	7	1.97	0.94–4.16	0.05

[a] Duration categorized in decades: 0–9, 10–19, 20–29, 30–39, ≥40 years or 0–9, 10–19, 20–29, ≥30 years.

[b] Categorized in exposed subjects involved in the corresponding activity according to 25th, 50th, 75th and 90th percentile: ≤9, 10–19, 20–39, 40–59, ≥60 hectares; [c] As prior but ≤4, 5–14, 15–29, 30–74, ≥75 hectares; [d] As prior but ≤4; 5–9, 10–19, ≥20 hectares; [e] As prior but ≤1, 2–4, ≥5 hectares; [f] As prior but ≤1, 2–9, 10–24, ≥25 hectares.

1.02–1.36), especially for the largest areas (≥60 hectares: HR 1.52, 95% CI 1.10–2.09; P for trend=0.06) (table 4). A significant lower risk of prostate cancer was observed for people working in wine cellars (HR 0.86, 95% CI 0.74-1.00) with a significant decreased risk for the longest duration (≥40 years: HR 0.68, 95% CI 0.47–0.98; P for trend=0.01). Almost all four tasks related to wheat/barley cultivation were associated with an elevated prostate cancer risk from 1.12 (95% CI 0.99–1.27) for sowing to 1.17 (95% CI 1.03–1.34) for pesticide use. Subjects involved in pesticide use on sunflowers had an increased risk of prostate cancer (HR 1.19, 95% CI 0.96–1.48). No task as binary variable was significantly associated with an elevated prostate cancer risk in rape production. However, participants using pesticide for ≥40 years showed a two-fold risk (HR 2.01, 95% CI 0.83–4.83). The three tobacco-related tasks were significantly or borderline significantly associated with an increased risk from 1.24 (95% CI 0.99–1.54) for pesticide use to 1.29 (95% CI 1.08–1.54) for harvesting. A significant increased risk was detected with increasing duration of sowing (P for trend=0.03). For pesticide use, a dose–response relationship was observed for duration (P for trend=0.02) and surface (≥5 hectares: HR 1.98, 95% CI 0.94–4.17; P for trend=0.04). Two of the three tasks related to fruit-growing increased the risk from 1.13 (95% CI 0.97–1.32) for harvesting to 1.19 (95% CI 0.97–1.45) for pesticide use. A longer duration of harvesting significantly increased the risk (P for trend=0.04). Pesticide application (HR 2.28, 95% CI 1.08–4.80) or harvesting (HR 1.97, 95% CI 0.94–4.16) ≥25 hectares of fruit trees increased the risk (respectively P for trend=0.02 and 0.05). Potato sowing (HR 1.25, 95% CI 1.08–1.45) and harvesting (HR 1.23, 95% CI 1.06–1.42) were significantly associated with an increased risk. Increased risks were also seen for two other potato cultivation tasks (seed treatment HR 1.18, 95% CI 0.89–1.56, pesticide use HR 1.19, 95% CI 1.00–1.41). For detailed results on crop-related tasks, see supplementary materials S2 (www.sjweh.fi/data_repository.php). No significant associations were observed for tasks related to corn, peas, and beets (data not shown).

Pesticide exposure

An elevated risk was observed for combined exposure to pesticides (application or re-entry tasks and harvesting) for several crops. For some of them, an increased risk was found for pesticide application (wheat/barley and sunflower) and harvesting and sowing of potatoes. For fruit-growing, only combined exposure to pesticides was associated with risk. Greater risks were observed among men who never wore protective gloves from 1.23 (95% CI 0.98–1.54) for potatoes to 1.44 (95% CI 1.10–1.88)

Table 5. Pesticide exposure and use of protective gloves in the AGRICAN cohort. Duration was categorized according to the median duration of cases. **BOLD** denotes statistically significant values (P<0.05). [HR=hazard ratio; 95% CI=95% confidence interval.]

	N cases	HR	95% CI	P for trend
Wheat/barley [a]				
Pesticide exposure [b]				
No pesticide exposure	80	1.03	0.81–1.31	
Pesticide application	62	1.10	0.84–1.43	
Re-entry and/or harvesting	101	0.98	0.79–1.22	
Both	481	**1.16**	**1.02–1.32**	
Using gloves [c]				
Never	255	**1.26**	**1.08–1.47**	
Sometimes	120	1.04	0.85–1.27	
Always	37	1.02	0.73–1.43	
Duration use of gloves [c]				0.14
Never	255	**1.26**	**1.08–1.48**	
0–24 years	32	0.92	0.64–1.32	
≥25 years	26	0.99	0.66–1.47	
Sunflower [a]				
Pesticide exposure [b]				
No pesticide exposure	2			
Pesticide application	11	1.10	0.61–2.00	
Re-entry and/or harvesting	13	0.87	0.50–1.50	
Both	78	1.14	0.90–1.43	
Using gloves [c]				
Never	46	1.33	0.99–1.79	
Sometimes	30	1.19	0.82–1.71	
Always	11	1.38	0.76–2.51	
Duration use of gloves [c]				0.46
Never	46	1.33	0.99–1.79	
0–9 years	8	**2.89**	**1.44–5.82**	
≥10 years	10	0.93	0.50–1.73	
Tobacco [d]				
Pesticide exposure [b]				
Pesticide application	3			
Re-entry and/or harvesting	69	1.18	0.92–1.51	
Both	82	1.25	1.00–1.57	
Using gloves [c]				
Never	41	1.28	0.94–1.75	
Sometimes	23	1.23	0.82–1.87	
Always	7	1.12	0.53–2.36	
Duration use of gloves [c]				0.61
Never	41	1.28	0.94–1.75	
0–19 years	6	1.34	0.60–2.99	
≥20 years	5	1.65	0.69–3.97	
Fruit-growing [d]				
Pesticide exposure [b]				
Pesticide application	6	0.96	0.43–2.15	
Re-entry and/or harvesting	115	0.97	0.79–1.18	
Both	125	1.21	0.98–1.48	
Using gloves [c]				
Never	58	**1.44**	**1.10–1.88**	
Sometimes	26	0.90	0.61–1.33	
Always	15	1.33	0.80–2.22	
Duration use of gloves [c]				0.32
Never	58	**1.44**	**1.10–1.88**	
0–24 years	8	1.01	0.50–2.03	
≥25 years	7	1.00	0.47–2.10	
Potatoes [d]				
Pesticide exposure [b]				
Pesticide application	10	1.03	0.55–1.93	
Re-entry and/or harvesting	100	1.18	0.96–1.46	
Both	169	**1.21**	**1.02–1.44**	
Using gloves [c]				
Never	87	1.23	0.98–1.54	
Sometimes	42	1.08	0.79–1.47	
Always	13	1.02	0.59–1.76	

[a] No pesticide exposure: only harvesting; pesticide application: seed treatment or pesticide use without sowing; re-entry and/or harvesting: sowing without seed treatment or pesticide use; both: pesticide application and re-entry and/or harvesting.

[b] Reference group=farmers not involved in the corresponding activity.

[c] Reference group=farmers who did not use pesticides on this crop.

[d] Pesticide application: seed treatment or pesticide use without sowing, pruning or harvesting; re-entry and/or harvesting: sowing, pruning or harvesting without seed treatment or pesticide use; both: pesticide application and re-entry and/or harvesting.

for fruit-growing, except for sunflowers (table 5). No relation was observed with duration of glove use for any of crops. A three-fold excess risk was observed for the shortest duration in sunflower cultivation.

Discussion

Overall, we found a small non-significant increased risk associated with farming and significant excesses for two of the five livestock studied (cattle and hog) and for specific tasks in 5 of the 13 crops studied (grassland, fruit-growing, tobacco, potatoes and wheat/barley).

The risk among cattle breeders was observed particularly in those performing milking and those applying insecticides on animals, and mainly in those with the largest number of animals. Two case–control studies conducted in New Zealand (13) and the USA (14) and the Agricultural Health Study (AHS) prospective cohort (19) also found a greater risk among cattle breeders. In the AHS, the authors found no convincing results for milking cows (19). In a retrospective cohort study, workers involved in cattle tick control in Australia were at increased risk of dying from prostate cancer. No effect was found when they were compared to other outdoor workers with a similar socioeconomic background but no exposure to insecticides (29). In the AHS, two insecticides used on cattle, permethrin and coumaphos, were associated with an elevated risk of prostate cancer among subjects with a family history of prostate cancer (30, 31). In our analyses, we were not able to investigate the type of insecticide used on cattle. We found an increased risk of prostate cancer for hog breeders, especially those having the largest stock. A borderline significant greater risk was observed for hog breeders in the AHS (19). However, our data do not suggest any excess risk for other types of livestock managers (poultry, horse and sheep, or goat breeders); notably there is a lack of effect of insecticide application on sheep, as in a previously historical cohort (23) but in contrast to the findings of Ewings et al (20) on sheep dipping. In fact, various methods may be used to apply insecticides on sheep but this information was not gathered in our enrolment questionnaire.

We observed a slight non-significant increased risk for pesticide use on crops (HR 1.10, 95% CI 0.97–1.25), in agreement with previous meta-analyses (8, 9). This association was greater among men who did not use protective gloves, but no conclusive associations were found with duration of use. The same pattern was observed for most specific crops. These findings support the need to encourage adequate use of personal protective equipment in preventive programs along with the communication of other important preventive messages that could reduce overall exposure to pesticides. To our knowledge, pesticide use on specific crops has never been studied according to the duration of the use of protective gloves.

We found a two-fold excess risk among subjects applying pesticides on ≥25 hectares and a nearly two-fold increase among fruit growers harvesting the same surface areas. No task was previously investigated but involvement in fruit-growing has been regularly associated with a prostate cancer risk (16–18) that may be two-fold higher (16). In France, fruit-growing accounts for <1% of the entire agricultural area but >5% of pesticide use. Treatment frequency may reach 17 times per year per hectare in fruit-growing (32). Pesticide exposure through re-entry tasks or harvesting is studied far less often although subjects performing re-entry tasks may be highly exposed to pesticides, specifically in fruit-growing (33). However, in our data, increased risk was more pronounced for harvesting than pruning. Haymaking on ≥60 hectares was significantly associated with prostate cancer, confirming the results obtained in a retrospective cohort study conducted in Canada on prostate cancer mortality among farmers involved in haymaking / fodder on >28 hectares (22). We also found an elevated risk among men involved in various tasks on tobacco as did Meyer et al (21) among Caucasian men harvesting tobacco. The risk was also increased for different tasks among men growing wheat or barley. Elsewhere, an elevated risk of dying from prostate cancer was associated with wheat production after adjustment for other crops (15). A significant association was observed between substantial grain dust exposure and prostate cancer without dose–response relationship (34). We did not find any increased risk associated with corn-growing, like Ewings et al (20), but they reported results on eight exposed cases. To our knowledge, this is the first time that the association between sunflower and rape production and prostate cancer risk has been studied. We found a non-significant two-fold excess risk for ≥40 years of pesticide application on rape but with only five exposed cases.

To date, we have not analyzed our data for ethnicity, but almost all the subjects were born in metropolitan France. We also have no family history of prostate cancer, although a statistically significant interaction was observed in the AHS between exposure to some active ingredients and family history of prostate cancer (30, 35). Our questionnaire included items about 18 different lifetime agricultural activities so we were able to make several comparisons. This large number of exposures led to a great number of comparison tests and some significant results, maybe by chance. Our strategy attempted to reduce this problem by studying not only dichotomous variables but also duration and intensity of exposure to reinforce the confidence in the results. Another purpose of using refine exposure was to decrease the possible correlation between activities or tasks. Indeed, male farmers in the cohort were involved, on average, in five agricultural activities in their life. When pairwise adjustments were performed to take into account possible false positive associations due to correlated activities, no significant changes in the estimates were observed. Combination of tasks were also investigated to take into account correlation. For instance, when combination of insecticide use on cattle and hay making was studied, increased risks of prostate cancer were still observed among farmers performing hay making, alone or in combination with insecticide use. We did not report increased risk among men using insecticides on cattle without performing hay making. Nevertheless, we could not formally exclude an effect of insecticide use on cattle as only a few people exclusively performed this task.

AGRICAN is a large prospective cohort including a wide variety of farm owners and workers. After only three years of follow-up, more than 1600 incident cases have allowed us to investigate dose–effect relationships with duration and size in detail for various exposure variables, even for infrequent agricultural activities and tasks. Our analyses made it possible to observe associations with specific tasks that the dichotomous activity variable used at the beginning of the analysis did not reveal. Fruit-growing is a good example since no association was observed with the dichotomous variable "ever involved in fruit-growing" but a two-fold increase was detected with the greater duration/size of some specific tasks. The agricultural activities in the questionnaire did not only concern pesticide use, so other tasks could be investigated including those involving pesticide exposure during re-entry tasks or harvesting where pesticide exposure may occur (36). Only one association with a decreased risk was observed: the duration of work in wine cellars. However, it disappeared after adjustment for individual characteristics.

Our study based on a large prospective cohort reports increased risk associated with raising cattle and hogs, and cultivating grassland and fruit with dose–response relationships not previously investigated in previous studies. Some findings are completely new, especially with respect to insecticide use on cattle, haymaking, and pesticide exposure in fruit-growing. It is now necessary to investigate the putative difference in etiology according to aggressiveness (35) or stage (37) of cancer. The main results of the study support the hypothesis of an association between pesticide exposure and prostate cancer risk through application on crops but also on animals or during re-entry tasks. The IARC recently classified some pesticides used both on crops or animals as carcinogenic (lindane) or probably carcinogenic (malathion) to humans. To date, no potential responsible agent was identified to explain the greater prostate cancer risk related to hay making and wheat/barley harvesting. We now intend to examine the role of specific pesticides using the crop-exposure matrix PESTIMAT (38).

Conflict of interest

The authors declare no conflicts of interest.

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